C2 D2 cont 31. A method selected from the group consisting of treating multidrug resistance, inhibiting p-glycoprotein, inhibiting MRP1, and combinations thereof, comprising administering to a mammal in need of such treatment or inhibition the composition according to Claim 24.

REMARKS

Applicants thank the Examiner for the consideration given the present application. Claims 2, 4, 5, 9, 11, and 18 – 31 are pending in the present application. The Examiner has rejected the claims based on 35 U.S.C. §§ 112 and 102(b).

The Rejections Under 35 U.S.C. § 112

The Examiner has rejected various of Applicants' claims under 35 U.S.C. § 112, either first or second paragraph. Applicants respond to each of these rejections, as follows:

First Rejection (Section 4 of the Office Action)

The Examiner has rejected Claims 2, 4, 5, 9, 11, 18 – 23, 25 – 27, 29, and 30 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. The Examiner states that use of the term "about" with reference to indivisible terms is indefinite.

Applicants respectfully traverse this rejection. Applicants remain unaware of any precedent which precludes the use of "about" in the cited instances. To the contrary, use of the term "about" to modify a quantitative description is commonplace throughout the chemical patent arts. Indeed, the Patent Office has routinely allowed and granted patents that contain claims utilizing the term "about" to modify a quantitative description, even where the quantitative description is an indivisible whole number. For example, Chatterjee, U.S. Patent No. 6,329,377, issued December 11, 2001 and Gangjee, U.S. Patent No. 6,221,872, issued April 24, 2001, both of which list Mukund J. Shah as the relevant Patent Office Examiner, utilize the term "about" to modify indivisible chemical chain lengths. The context of usage in these granted patents is no different relative to Applicants' current usage. Indeed, the Examiner is imposing prejudice with respect to the present patent application in improperly disregarding rules of practice that are routinely utilized in the examination of patent applications.

The Examiner cites *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200 Fed. Cir. 1991, in support of the rejection. In doing so, the Examiner cites various passages from *Amgen* that relate to the specific factual circumstances in that case. For example, in *Amgen*, the Federal Circuit found that the existence of close prior art, coupled with testimony offered by the parties, was determinative in finding the relevant claims indefinite due to the use of the term "about." However, in doing so, the Examiner fails to relate the relevance of the *Amgen* prior art issue, as well as the *Amgen*

testimony, to Applicants' claimed subject matter. Indeed, none of these factual circumstances are present with respect to the patent application currently before the Examiner.

Moreover, the Examiner fails to recognize that the Federal Circuit expressly limited the decision in *Amgen* to the specific facts set forth therein. Importantly, the Federal Circuit states that "[i]n arriving at this conclusion, we caution that our holding that the term "about" renders indefinite claims 4 and 6 should not be understood as ruling out any and all uses of this term in patent claims." See *Amgen*, p. 1218 (emphasis added).

As has been stated, and as the Examiner is compelled to recognize and accept, use of the term "about" to modify various claim limitations has been found to be routinely acceptable in the chemical arts. See *W.L. Gore & Associates v. Garlock, Inc.*, 842 F.2d 1275 (1988). In rejecting this established rule, it appears that the Examiner is attempting to resolve issues that have been found to be matters of law reserved for the courts through procedures such as *Markman* hearings. See *Markman v. Westview Instruments, Inc.*, 52 F.3d 967 (1996). In doing so, particularly since the Examiner has failed to present a nexus between the present rejection and any prior art issue (as with *Amgen*), the Examiner is respectfully acting outside the scope of his authority.

For example, the Examiner is compelled to recognize the procedures and holding set forth in *Pall Corp. v. Micron Separations, Inc.*, 66 F.3d 1211 (Fed. Cir. 1995). In *Pall*, the Federal Circuit did not dispute whether use of the term "about" was appropriate, but rather recognized that claim construction was the issue, an issue which was a matter of law settled by the relevant court in view of extrinsic and other evidence. The Federal Circuit stated:

> The district court, construing the term 'about 5:1 to about 7:1,' observed that the word 'about' does not have a universal meaning in patent claims, and that the meaning depends on the technological facts of the particular case. We have so held. . . . [citing *W.L. Gore & Associates v. Garlock, Inc.*, 842 F.2d 1275 (1988)]. . . . The determination of whether the literal meaning or cope of 'about 5:1 to about 7:1' includes 4:1 is a matter of claim construction, a question of law for decision *de novo* by this court. The use of the word 'about,' avoids a strict numerical boundary to the specified parameter. Its range must be interpreted in its technologic and stylistic context. . . . Extrinsic evidence of meaning and usage in the art may be helpful in determining the criticality of the parameter, and may be received from the inventor and others skilled in the field of the invention."

See *Pall*, p. 1217.

Moreover, the Federal Circuit continues to recognize the appropriate use of the term "about" in a granted patent claim, and the role of the courts with respect to interpretation. *Modine Manufacturing Co. v. U.S. International Trade Commission*, 75 F.3d 1545 (Fed. Cir. 1996) stated:

> The specification uses the qualifier "about," and also states that the optimum hydraulic diameter varies with the conditions. Such broadening usages as "about" must be given reasonable scope; they must be viewed by the decisionmaker [the

> court, *e.g.*, pursuant to a *Markman* hearing] as they would be understood by persons experienced in the field of the invention. . . . Although it is rarely feasible to attach a precise limit to "about," the usage can usually be understood in light of the technology embodied in the invention.

See *Modine*, p. 1554.

In view of binding precedent, therefore, Applicants' claims duly meet the requirements of 35 U.S.C. § 112, second paragraph. The Examiner is compelled to follow the ready acceptance of the term "about" by the Federal Circuit, particularly absent the precise factual issues present in *Amgen*, with the understanding that it is not the Examiner's role to interpret the precise scope of the claim. The Examiner should recognize that these matters have been clearly reserved for the courts, a responsibility which is not properly the Examiner's concern in this instance. Respectfully, it is for all of the above reasons that the Examiner should withdraw the rejection of Claims 2, 4, 5, 9, 11, 18 – 23, 25 – 27, 29, and 30 under 35 U.S.C. § 112, second paragraph.

Second Rejection (Section 5 of the Office Action)

The Examiner has rejected Claims 29 – 31 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which is regarded as the invention. The Examiner states that the phrase "and combinations thereof" is indefinite due to the use of the term "combinations" as a plural term, and due to the Examiner's conclusion that Applicants cannot treat multidrug resistance without inhibiting transport protein activity.

While Applicants traverse this rejection, Applicants have made amendments to each of Claims 29 – 31 which render this rejection moot. In particular, Applicants have amended these claims to recite the specific transport proteins p-glycoprotein and MRP1. Support for these amendments is found at pages 1 and 51 – 53 of the specification, as well as throughout. In view of these amendments, use of the term "combinations" is indeed appropriate as a plural term and the rejection is now moot. Applicants therefore respectfully request that the Examiner withdraw the present rejection of Claims 29 – 31 because the claims, particularly as amended herein, are indeed definite.

Third Rejection (Section 6 of the Office Action)

The Examiner has rejected Claims 2, 4, 5, 9, 11, 18 – 23, 25 – 27, 29, and 30 based on 35 U.S.C. § 112, first paragraph. In particular, the Examiner states that the terms 'biohydrolyzable amide,' 'biohydrolyzable ester,' and 'biohydrolyzable imide' are "unduly functional." Applicants continue to traverse this rejection. However, in the interest of advancing this issue, Applicants propose use of claim language deemed acceptable (on amendment) in a companion case, U.S. Patent Application Serial No. 09/740,643, now issued as U.S. Patent No. 6,376,514 (April 23, 2002) out of

Group Art Unit 1624 (as proposed by Primary Examiner Alan Rotman (supervisor to Ms. Rita Desai) during a telephonic interview. In particular, such language is as follows:

> [A compound having the recited structure] "or an optical isomer, diastereomer, enantiomer, pharmaceutically-acceptable salt, amide, ester or imide susceptible to being cleaved *in vivo* by a mammalian subject to yield the compound of the claim thereof . . ."

See Claim 2, U.S. Patent No. 6,376,514, companion case to present application.

Claim 18, upon which all other rejected claims depend, has been amended herein to utilize language of this type. This language overcomes the concerns raised by the Examiner. In particular, use of this language makes clear that the active compounds recited in the base structure of Claim 18 must be yielded *in vivo*, by a mammal, upon mammalian administration of such amide, ester or imide. Applicants therefore respectfully request that the Examiner consider the amendment herein, and duly withdraw the rejection of Claims 2, 4, 5, 9, 11, 18 – 23, 25 – 27, 29, and 30 based on such amendment.

Fourth Rejection (Section 7 of the Office Action)

The Examiner has rejected Claims 2, 4, 5, 9, 11, 18 – 23, 25 – 27, 29, and 30 based on enablement, stating that the specification is only enabling for compounds of Claim 18 wherein R^5 is 5-quinolinyloxy.

In support of this rejection, the Examiner states that "[c]ompounds *made and tested* represent the scope of claim 24, not claim 18" (emphasis added). Respectfully, this characterization is improper. Indeed, since *the Examiner cannot be aware of which compounds Applicants have or have not "made and tested,"* the Examiner appears to have based the rejection upon Applicants' own disclosure of particularly preferred limitations as set forth in the examples, including those which have been most often exemplified in the specification. However, there is no requirement that a patent applicant can claim only what is "made," "tested," or even exemplified. Applicants stress that there is absolutely no requirement under the patent laws that a patent applicant must disclose each and every compound made and tested, nor is there a requirement that the breadth of an allowed claim should be limited to those compounds specifically exemplified in a patent application. If the Examiner continues to rely upon statements such as "[c]ompounds made and tested represent the scope of claim 24, not claim 18," it is requested that the Examiner offer Applicant some basis in law that requires that all compounds within the scope of Claim 18 must be specifically exemplified in the patent application.

In framing the rejection in this flawed manner, the Examiner has failed to consider the proper test for enablement as set forth in MPEP 2164.08, which provides two stages of inquiry: 1) to

determine how broad the claim is with respect to the disclosure; and 2) to determine if one skilled in the art is enabled to make and use the entire scope of the claimed invention without undue experimentation. The Examiner has acknowledged that the claim is no broader than the specification. Accordingly, the second stage of this inquiry remains to be addressed.

With regard to this second stage of inquiry, it appears that the Examiner is not basing this rejection in view of requirements regarding how to make the present compounds and compositions. Accordingly, Applicants now focus their response with respect to the requirement relating to "how to use." Applicants must respond to this rejection in view of the accepted legal standards for enablement. Indeed, there is no basis in patent law that requires an applicant to do more than describe the various inventive compounds, either generally or specifically, and disclose their putative use, without relying on undue experimentation (some necessary experimentation is appropriate). See MPEP 2164.01(c).

Referring therefore to the Office Action, the Examiner has stated that: (1) there is "no reasonable basis for the assumption that the myriad of compounds embraced [by Claim 18] will all share the same biological properties," (2) the claimed structures are "chemically non-equivalent," and (3) "there is no basis in the prior art for assuming in the non-predictable art of cancer chemotherapy that structurally dissimilar compounds will have such activity." Applicants do not understand the term "chemically non-equivalent" and are unable to respond to this comment; however, what is clear is that the Examiner has imposed a restriction requirement that groups the compounds of Claim 18 into one examinable class (defined 1-carbonylpiperidines having the recited functional groups). Accordingly, the Examiner has acknowledged on the record that the compounds currently under examination bear a common relation.

Moreover, requiring a "basis in the prior art for assuming that . . . structurally dissimilar compounds will have [MDR] activity" is not an appropriate basis for examining Applicants' claims. This statement is, respectfully, inappropriate - would not teaching in the prior art regarding such substitution require an obviousness rejection? Indeed, is not suggestion in the prior art tantamount to a rejection based on obviousness? Is the Examiner rejecting Applicants' claims because there is actually no suggestion of Applicants' invention in the prior art? Applicants respectfully request clarification of this point with a grounded basis in the applicable law.

Even further, despite the Examiner's characterization, Applicants' specification is not without guidance to the ordinarily skilled practitioner. Again addressing the requirement relating to "how to use," Applicants have provided more than adequate description in this regard. Applicants have provided numerous pages of examples of exemplary compounds, *as well as descriptions of preferred substituent groups for almost every moiety of the claimed structures* (see, for example, the numerous disclosures of preferred embodiments disclosed on pages 7 – 13 of the specification, keeping in mind again that there is no basis in law that requires that a patent applicant is limited to preferred embodiments of an invention). These examples and preferred embodiments are merely illustrative of

various ways in which the claimed compounds can be used – there is no statutory requirement for the disclosure of a specific example since a patent specification is not intended nor required to be a production specification. See MPEP 2165.02 (II) and *In re Gay*, 135 USPQ 311 (CCPA 1962).

Coupled with Applicants' disclosure regarding preferred limitations, embodiments, and specific examples, Applicants have further described various assays that may be utilized by the ordinarily skilled artisan in order to determine biological activity. For example, Applicants disclose a MDR1 ATPase assay, citing Sarkadi *et al.*, "Expression of the Human Multidrug Resistance cDNA in Insect Cells Generates High Activity Drug-stimulated Membrane ATPase," *The Journal of Biological Chemistry*, Vol. 267, No. 7, pp. 4854 – 4858 (1992) ("Sarkadi"). As set forth in Sarkadi, "the ability of the various drugs [*i.e.*, those tested in the assay] to stimulate the ATPase corresponds to their previously observed affinity for this transporter [p-glycoprotein]." See Sarkadi, p. 4854. Moreover, inhibition of this transporter (p-glycoprotein) has been disclosed by Applicants at page 51 ("Reversal Assay"). Even further, other literature confirms the importance of inhibition of p-glycoprotein with respect to treatment of MDR. For example, Saeki *et al.*, "Human P-glycoprotein Transports Cyclosporin A and FK-506," *The Journal of Biological Chemistry*, Vol. 268, No. 9, pp. 6077 - 6080 (1993) discloses the importance of p-glycoprotein, and its capacity to transport chemotherapy agents away from the site of action as well the importance of p-glycoprotein as necessary to free up the chemotherapy agent. The various *in vitro* assays available for assessing the present inventive compounds are therefore adequately correlated to MDR and provide even further instruction to the ordinarily skilled artisan.

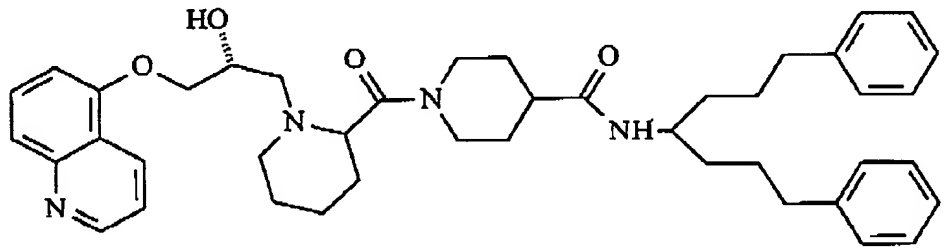
Accordingly, while the state of art may be relatively unpredictable relative to other arts, this element of unpredictability should not preclude Applicants from claiming the subject matter to which they have described and are entitled. The reason for this is that Applicants have provided the ordinarily skilled artisan with ample disclosures regarding the recited compounds, as well as methods for testing the efficacy of such compounds. Indeed, Applicants have provided broad disclosures, numerous preferred embodiments, and specific examples, all of which differ in various respects, as well as numerous assays to test the activity of the described compounds.

For all of the above reasons, Applicants therefore respectfully request that the Examiner reconsider and withdraw the rejection of Claims 2, 4, 5, 9, 11, 18 – 23, 25 – 27, 29, and 30 based on enablement, because Applicants have provided ample directive disclosure in this respect.

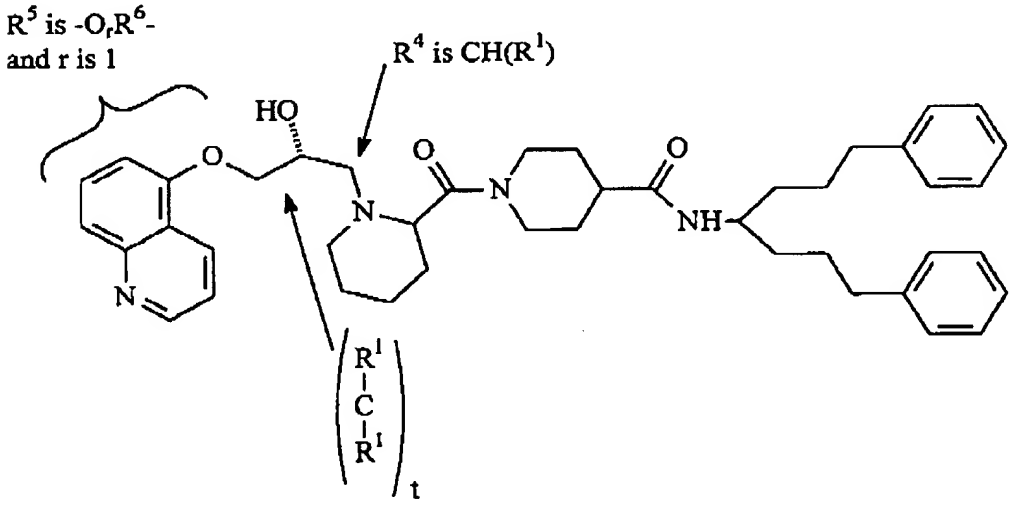
Fifth Rejection (Section 8 of the Office Action)

The Examiner has rejected Claims 2, 4, 5, 9, 11, 18 – 23, 25 – 27, 29, and 30 under 35 U.S.C. § 112, first paragraph. The Examiner states that "[t]he proviso in the last line of section (f) of claim 18, concerning the relationship between R^4 and R^5 lacks description. Nowhere in the specification is such a relationship linking the description between the two radicals described. The concept of linking the value of r to the specific divalent radical present as R^4 is not present."

Applicants traverse this rejection. In amending the claims to require the relevant proviso (*i.e.*, "with the proviso that wherein R^4 is $-CH(R^1)-$ and R^5 is $-O_rR^6-$ then r is 1") in Applicants' previous response dated March 19, 2002, Applicants noted that this proviso was fully supported by the specification such as, for example, at Example 7 at page 34. Applicants maintain this assertion. Full support for this proviso is indeed set forth at this location of the specification; indeed, Example 7, page 34 of the present specification describes the following compound:



Each element of the relevant proviso is described by the structure, as is seen from the following notations:



In particular, in this structure set forth in the specification, R^4 is $-CH(R^1)-$, R^5 is $-O_rR^6-$ and r is 1, thereby describing each and every element of the relevant proviso. Accordingly, the proviso as set forth in Claim 18 is fully described in the specification. Applicants therefore request that the Examiner withdraw the rejection of Claims 2, 4, 5, 9, 11, 18 – 23, 25 – 27, 29, and 30 under 35 U.S.C. § 112, first paragraph.

Sixth Rejection (Section 9 of the Office Action)

The Examiner has rejected Claims 29 – 31 under 35 U.S.C. § 112, first paragraph. The Examiner states that while the specification is enabling for treatment of multidrug resistance (compare this statement by the Examiner with Section 7 of the Office Action regarding enablement, discussed immediately above), the specification does not reasonably provide enablement for inhibition of transport protein activity generally. Applicants respectfully traverse this rejection, particularly based on the various assays described in the specification (as explained above). As has been explained (both by Applicants and the literature generally), dysfunctional transport protein activity has been implicated with respect to the root cause of MDR.

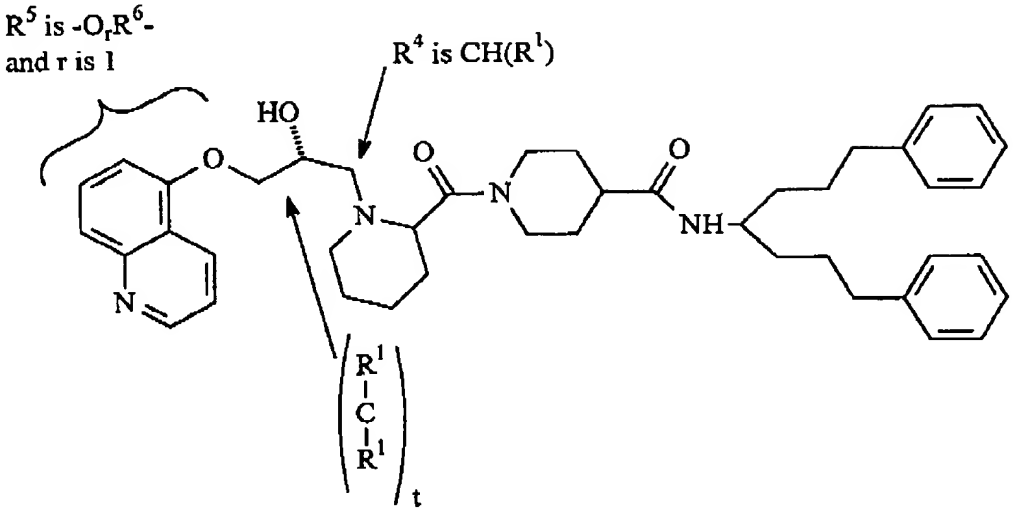
However, in the interest of progressing the various issues presented by the Examiner, Applicants have amended Claims 29 – 31 to reference inhibition of p-glycoprotein or MRP1 rather than transport proteins generally (see specification at page 1 and throughout for discussion of p-glycoprotein and MRP1, both of which are commonly understood in the art). Indeed, Applicants have asserted the nexus between MDR and these specific transport proteins, and has provided ample direction for measurement of inhibition of such specific transport proteins (see specification at pages 51 – 53). Support for these amendments is therefore found at pages 1 and 51 – 53 of the specification, as well as throughout.

In view of these amendments, it is asserted that Claims 29 – 31 are indeed enabled by the specification. Applicants therefore respectfully request that the Examiner withdraw this rejection because the requisite elements with respect to enablement have been met.

The Rejection Under 35 U.S.C. § 102(b)

The Examiner has rejected Claims 2, 4, 11, 18, and 25 – 27 under 35 U.S.C. §102(b) based on Xue *et al.*, WO 99/65867, published December 23, 1999 (herein referred to as "Xue"). The Examiner states that although the amendments presented by Applicants in their response dated March 19, 2002 overcome the rejection in terms of anticipation, the rejection is maintained based on the "new matter" rejection set forth in the Fifth Rejection of the Office Action (Section 8 of the Office Action).

As Applicants have explained above with respect to this Fifth Rejection, the proviso set forth in Claim 18 that excludes the subject matter of Xue is adequately described in the specification and therefore does not include new matter. In particular, as described above and reiterated here, full support for this proviso is set forth at Example 7, page 34 of the present specification. Indeed, each element of the relevant proviso is described by the structure, as is seen from the following notations:



In particular, in this structure set forth in the specification, R^4 is $-CH(R^1)-$, R^5 is $-O_rR^6-$ and r is 1, thereby describing each and every element of the relevant proviso. Accordingly, the proviso as set forth in Claim 18 is fully described in the specification. Because the relevant proviso is not new matter, it is respectfully requested that the Examiner withdraw the present rejection under 35 U.S.C. § 102(b) and promptly allow the present claims.

CONCLUSION

Applicants therefore respectfully request that the Examiner withdraw the rejections under 35 U.S.C. §§ 102(b) and 112 and allow Claims 2, 4, 5, 9, 11, and 18 – 31 as presented herein. If the Examiner believes that personal contact would be beneficial for disposition of the present application, the Examiner is respectfully requested to contact the undersigned.

Respectfully submitted,

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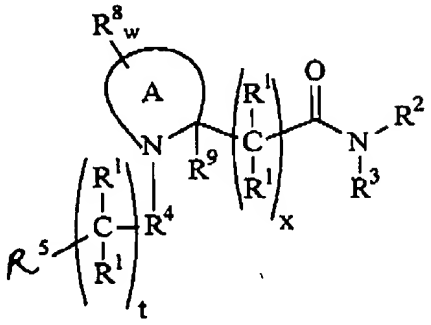
Telephone: 513-622-0159

August 29, 2002
Customer No. 27752

Version with Markings to Show Changes Made

Claim 18 has been amended as follows:

18. A compound having the structure:



or an optical isomer, diastereomer, enantiomer, pharmaceutically-acceptable salt, ~~biohydrolyzable~~ amide, ~~biohydrolyzable~~ ester, or ~~biohydrolyzable~~ imide susceptible to being cleaved *in vivo* by a mammalian subject to yield the compound thereof, wherein:

(a) w is 0 to about 6, x is 0 to about 10, and t is 0 to about 6;

(b) A is a substituted heterocyclic group having about 4 to about 9 members;

(c) R^1 is selected from the group consisting of a hydrogen atom, a hydroxyl group, a hydrocarbon group, a substituted hydrocarbon group, a heterogeneous group, a substituted heterogeneous group, a carbocyclic group, a substituted carbocyclic group, a heterocyclic group, a substituted heterocyclic group, an aromatic group, a substituted aromatic group, a heteroaromatic group, and a substituted heteroaromatic group;

(d) R^2 and R^3 are bonded together to form a substituted piperidyl;

(e) R^4 is selected from the group consisting of $-S(O)_2-$, -C(O)-C(O)-, and $-CH(R^1)-$;

(f) R^5 is selected from the group consisting of $-NR^6(R^7)-$ and $-O_rR^6-$, wherein r is 0 or 1; with the proviso that wherein R^4 is $-CH(R^1)-$ and R^5 is $-O_rR^6-$ then r is 1;

(g) R^6 is selected from the group consisting of a hydrocarbon group, a substituted hydrocarbon group, a heterogeneous group, a substituted heterogeneous group, a carbocyclic group, a substituted carbocyclic group, a heterocyclic group, a substituted heterocyclic group, an aromatic group, a substituted aromatic group, a heteroaromatic group, and a substituted heteroaromatic group; and

R^7 is selected from the group consisting of a hydrogen atom and R^6;

(h) R^8 is selected from the group consisting of a hydrocarbon group, a substituted hydrocarbon group, a heterogeneous group, a substituted heterogeneous group, a carbocyclic group, a substituted carbocyclic group, a heterocyclic group, a substituted

heterocyclic group, an aromatic group, a substituted aromatic group, a heteroaromatic group, and a substituted heteroaromatic group; and

(i) R^9 is selected from the group consisting of a hydrogen atom and a hydrocarbon group.

Claim 29 has been amended as follows:

29. A method selected from the group consisting of treating multidrug resistance, inhibiting ~~transport protein activity~~p-glycoprotein, inhibiting MRP1, and combinations thereof, comprising administering to a mammal in need of such treatment or inhibition the composition according to Claim 18.

Claim 30 has been amended as follows:

30. A method selected from the group consisting of treating multidrug resistance, inhibiting ~~transport protein activity~~p-glycoprotein, inhibiting MRP1, and combinations thereof, comprising administering to a mammal in need of such treatment or inhibition the composition according to Claim 11.

Claim 31 has been amended as follows:

31. A method selected from the group consisting of treating multidrug resistance, inhibiting ~~transport protein activity~~p-glycoprotein, inhibiting MRP1, and combinations thereof, comprising administering to a mammal in need of such treatment or inhibition the composition according to Claim 24.